Complete Summary

GUIDELINE TITLE

Concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer (excluding nasopharynx).

BIBLIOGRAPHIC SOURCE(S)

Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L, Cancer Care Ontario Practice Guidelines Initiative (CCOPGI). Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. Head Neck 2001;23:579-89. [51 references]

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer (excluding nasopharynx) [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2000 Mar [online update]. Various p. (Practice guideline; no. 5-6a). [48 references]

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SCOPE

DISEASE/CONDITION(S)

Locally advanced stage III or stage IV squamous cell carcinoma of the head and neck (SCHNC) (excluding nasopharynx)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To determine if the addition of concomitant chemotherapy to radiotherapy, the initial modality of choice for cure, is effective in improving survival (with acceptable toxicity) in patients with locally advanced squamous cell head and neck cancer (SCHNC) compared with conventional therapy alone

TARGET POPULATION

Patients with newly diagnosed stage III or IV squamous cell cancer of the head and neck who are being considered for radiotherapy as the definitive modality for curative intent, and for whom combined radiation and chemotherapy can be tolerated in the judgment of the treating oncologist

INTERVENTIONS AND PRACTICES CONSIDERED

1. Concomitant chemotherapy regimens, including:
    - Single agents, such as cisplatin/carboplatin, bleomycin, 5-fluorouracil, infusional 5-fluorouracil, mitomycin C, methotrexate
    - Combination chemotherapy regimens without platinum compounds
    - Combination chemotherapy regimens with platinum compounds
2. Radiotherapy fractionation, including the following schedules:
    - Conventional continuous
    - Non-conventional, such as accelerated, hyperfractionated, or split-course

MAJOR OUTCOMES CONSIDERED

Primary outcome

- Mortality

Secondary outcome

- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1970 to December 1999), CANCERLIT (1983 to October 1999), HEALTHSTAR (1975 to November 1999), the Cochrane Library (Issue 4, 1999), and relevant conference proceedings were searched. "Head and neck neoplasms" (Medical subject heading [MeSH]) was combined with "combined modality therapy" (MeSH), and each of the following phrases used as text words: "concomitant or combined", "radiotherapy", "chemotherapy", "surgery", "malignant neoplasms". These terms were then combined with the search terms for the following study designs: randomized trials, systematic review, meta-analysis, double-blind method, practice guideline, and review. Citation lists of relevant studies were used to identify additional trials, as were the private files of oncologists. The Physician Data Query (PDQ) clinical trials database (U.S. National Cancer Institute) was searched for reports of ongoing trials. This literature search was updated in March 2000 (MEDLINE through March 2000, CANCERLIT through February 2000, HEALTHSTAR through February 2000 and the Cochrane Library Issue 1, 2000).

NUMBER OF SOURCE DOCUMENTS

30 studies located; 18 studies meeting eligibility criteria

4 meta-analyses of trials and 2 systematic reviews

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Trial eligibility

For this analysis, all forms of concomitant schedules were included, but subgroup analysis (stratification) was used to explore possible differences related to either different radiotherapy fractionation schedules or different chemotherapy schedules.

To be eligible, trials had to be randomized and the control arm could not include chemotherapy, patients had to be newly diagnosed with stage III or IV disease without distant metastases, radiotherapy had to be the definitive initial treatment

modality, adequate doses of radiotherapy had to be used in both arms (equivalent to at least 65 Gy total dose [using conventional continuous fractionation] to the primary lesion), fewer than 20% of patients could have nasopharynx cancer, and the analysis had to include survival as an outcome with an 'intention-to-treat' approach. Trials involving the use of radiation sensitizing agents that were not anti-neoplastics were excluded. Other reasons for exclusion include: inadequate radiotherapy doses in the control arm; a study population not relevant to the question; very unconventional radiotherapy fractionation schedules; and an inappropriate analysis of responders only in one trial.

Clinical outcome and pooling of results

Mortality was the primary outcome of interest. The study results were pooled using Metaanalyst[0.988] software provided by Dr. Joseph Lau (Boston, MA). Results are expressed as odds ratios (OR) with 95% Confidence Intervals (CI), where an odds ratio for mortality less than one indicates that the experimental treatment (concomitant therapy) improved survival compared with the control (radiotherapy alone). Conversely, an odds ratio greater than one suggests that patients in the control group experienced better survival. The absolute risk difference (RD) was also calculated. Because of concerns around trial heterogeneity, the random effects model was used as the more conservative estimate of effect.

In squamous cell head and neck cancer, local control is also considered an important clinical outcome because of the morbidity associated with local recurrence. Many clinical oncologists would be inclined to use a therapy that reduced the probability of, or delayed, local recurrence - even if survival was equivalent to standard treatment. For this systematic overview, local control was not examined pending the need for such an analysis after examining the survival data. The analyses showed that the results based on mortality seemed to make a separate analysis on local control unnecessary.

An important intergroup trial of single-agent weekly cisplatin by Haselow (N=319 evaluable) was closed in 1987, but at the time of guideline preparation the detailed mortality data had not been reported. The only available publication indicates no difference between the treatment arms, both of which included conventional radiotherapy. For the present analyses, the guideline developers have assumed exact equivalence of the treatment arms and have performed a sensitivity analysis with and without this trial [additional data on the Haselow study were made available through the publication of the MACH-NC individual patient data meta-analysis but could not be incorporated into this analysis].

Studies were stratified for the pooled analysis according to:

i. The radiotherapy fractionation schedule used in the control arm (conventional continuous radiotherapy versus non-conventional, e.g., accelerated, hyperfractionated, split-course);
ii. Whether radiotherapy schedules in the control and experimental arms were the same;
iii. Chemotherapy regimen used:
    - Single agent (cisplatin/carboplatin, bleomycin, 5-fluorouracil, mitomycin C) versus multiple agent
    - Platinum-containing regimens versus other

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The discussion of the guideline and practitioner feedback led the Group to address the issue of the acceptability of recommending that standard, continuous fractionated radiotherapy alone can be justified in light of the current evidence for concomitant treatment. There was a strong consensus that the weight of the evidence should allow for a stronger statement in the recommendations on this matter. While the Disease Site Group (DSG) members were wary of making a recommendation that would change standard practice, it was decided to strengthen the recommendation. This was done by ensuring that oncologists who were considering standard, conventional fractionated radiotherapy (RT) alone were aware of their obligation to inform patients of this guideline and of the results of trials of concomitant chemotherapy plus radiotherapy.

There was also discussion of the emerging data related to the use of accelerated fractionated radiotherapy (Radiation Therapy Oncology Group [RTOG] protocol), and the knowledge that at least one highly credible Ontario cancer institution is recommending accelerated fractionation RT. It was decided that, at this time, the data for concomitant chemotherapy (CT) and RT are at least as good as the data for accelerated fractionation, and the body of evidence is much larger.

Clinical recommendations should take into account the toxicity profiles of different concomitant regimens. The analyses suggest that hyperfractionated RT with CT produces clinically important excess toxicity compared with conventional RT plus CT. Until the issues identified above are settled through more research and further regression analyses, it seems reasonable to recommend that the best tolerated cisplatin (CP)-based regimens be used that have shown a benefit in individual trials.

A separate guideline is being prepared on the use of different fractionation schedules for the radiation treatment of this patient population. The preliminary analyses do not challenge the recommendations for concomitant treatment in this guideline. The Disease Site Group members decided that it would be most useful to consolidate the guidelines on concomitant CT, neoadjuvant CT and the use of altered RT fractionation regimens into one guideline to produce a comprehensive recommendation for the treatment of patients with locally advanced head and neck cancer in whom radiotherapy is considered the definitive treatment modality of choice. This consolidated document will be released once all individual guidelines have been completed.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 42 practitioners in Ontario (18 medical oncologists and 24 radiation oncologists). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Provincial Head and Neck Cancer Disease Site Group.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Concomitant chemotherapy with conventional fractionated radiotherapy should be the treatment of choice for patients with advanced squamous cell head and neck cancer.
- At this time there are insufficient data to recommend the use of concomitant chemotherapy with altered fractionation schedules.
- The choice of concomitant therapy should take into account the toxicity produced by various regimens and the convenience of treatment administration. An examination of individual trial results and toxicity profiles using concomitant cisplatin-based treatment suggests that reasonable options outside a clinical trial, given all the circumstances, include either:
    - Single-agent daily cisplatin or carboplatin with conventional radiotherapy, or
    - Alternating split-course radiotherapy with cisplatin plus infusional 5-fluorouracil

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Four relevant systematic reviews involving meta-analyses of trials of concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer were found. Two other relevant systematic overviews were also located. One assessed the toxicity difference between concomitant chemotherapy and radiotherapy

compared with radiotherapy alone from the Munro overview, and the other was a systematic overview of four trials of conventional versus hyperfractionated radiotherapy in squamous cell head and neck cancer and other cancers.

There were 30 studies located through the literature review. Table 2A (Appendix A) in the original guideline document lists their eligibility status, reason for exclusion, and their key features according to the stratification criteria. Table 3 in the original guideline document lists the 18 studies meeting the eligibility criteria.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Concomitant chemotherapy with radiotherapy improves survival in patients with squamous cell head and neck, cancer compared with radiotherapy alone.

POTENTIAL HARMS

Adverse effects of platinum-containing chemotherapy regimens include stomatitis, hematologic effects, weight loss, and xerostomia.

Toxicity for concomitant chemotherapy plus radiotherapy compared with radiotherapy alone is more pronounced with the hyperfractionated radiotherapy regimens where the main observation is enhancement of the side effects normally associated with radiotherapy (stomatitis and weight loss). On the other hand, the toxicity associated with daily, low-dose single-agent cisplatin or carboplatin, or with split-course, alternating radiotherapy is less marked and confined mainly to hematologic toxicity. The use of 3 cycles of 4 days of carboplatin/infusional 5-fluorouracil with conventional radiotherapy in the positive trial by Calais et al (Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91:2081-6) also produced substantially more toxicity than radiotherapy alone.

Note: Reporting of late toxicities is often incomplete and difficult to factor into any clinical recommendation based on published evidence.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Full disclosure to patients with advanced squamous cell cancer of the head and neck should include a discussion of the results of concomitant chemotherapy and radiotherapy, recognizing that patient preference, physician judgment and toxicity issues are important factors in determining clinical management for individual patients.
- A separate guideline is being prepared on the use of different fractionation schedules for the radiation treatment of this patient population. The preliminary analyses do not challenge the recommendations for concomitant treatment in this guideline. The Disease Site Group members decided that it

would be most useful to consolidate the guidelines on concomitant chemotherapy, neoadjuvant chemotherapy and the use of altered radiotherapy fractionation regimens into one guideline to produce a comprehensive recommendation for the treatment of patients with locally advanced head and neck cancer in whom radiotherapy is considered the definitive treatment modality of choice. This consolidated document will be released once all individual guidelines have been completed.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L, Cancer Care Ontario Practice Guidelines Initiative (CCOPGI). Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. Head Neck 2001;23:579-89. [51 references]

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer (excluding nasopharynx) [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2000 Mar [online update]. Various p. (Practice guideline; no. 5-6a). [48 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Feb 23 (updated online 2000 Mar)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Head and Neck Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Head and Neck Cancer Disease Site Group Members: Dr. D. I. Hodson, (Chair), Radiation Oncologist; Dr. S. Archibald, Surgeon; Dr. G. Browman, Medical Oncologist; Dr. C. Cripps, Medical Oncologist; Dr. J. Davidson, Surgeon; Dr. P. Dixon, Radiation Oncologist; *Dr. L. Eapen, Radiation Oncologist; Dr. R. Gilbert, Surgeon; Dr. L. Grimard, Radiation Oncologist; Dr. S. Gulavita, Radiation Oncologist; Dr. J. A. Hammond, Radiation Oncologist; Ms. C. Ivasiuk, Community Representative; Dr. R. J. Mackenzie, Radiation Oncologist; Dr. W. Matthews, Surgeon; Dr. H. Prichard, Radiation Oncologist; Dr. K. Schneider, Radiation Oncologist

Resource group members working with the Head and Neck Cancer Disease Site Group: Faculty: Dr. G. Browman; Staff: Ms. N. Bestic*, Ms. M. Johnston*, Ms. L. Zuraw

*Members that have completed term with the Head and Neck Cancer Disease Site Group

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Head and Neck Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The guideline developer instituted a new format for their guidelines and evidence summaries: A SUMMARY of the original Practice Guideline or Evidence Summary,

integrated with the most current information, replaces the ABSTRACT, RECOMMENDATION, BRIEF REPORT and EVIDENCE UPDATE.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Practice Guidelines Initiative Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Not available at this time.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer (excluding nasopharynx). Summary. Toronto (ON): Cancer Care Ontario (CCO). 2000 Mar. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

The following companion guidelines are also available:

- Accelerated radiotherapy for locally advanced squamous cell carcinoma of the head and neck. Toronto (ON): Cancer Care Ontario (CCO); 2000 Nov. Various p. (Practice guideline; no. 5-6c).
- Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 13 p. (Practice guideline report; no. 5-6b). (see the National Guideline Clearinghouse summary).

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 5, 2002. The information was verified by the guideline developer as of July 8, 2002.

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